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(19) (CA) **CANADIAN PATENT** (12)

(54) PROCESS FOR THE PRODUCTION OF SUSTAINED RELEASE  
PHARMACEUTICAL COMPOSITION OF SOLID MEDICAL  
MATERIAL

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# ABSTRACT OF THE DISCLOSURE

Sustained release pharmaceutical compositions of solid medical material contains the amorphous solid medical material, polyethylene oxide, and at last one basic substance selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate metal acrylic acid copolymer, 2-methyl-5-vinylpyridinemethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acid. Optionally, the composition may further contain another basic substance selected from the group consisting of surface active agent, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid ester and vegetable oil. According to another aspect of the invention, a sustained release pharmaceutical composition of amorphous nicardipine compounded with polyethylene oxide is provided.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE ARE CLAIMED IS DEFINED AS FOLLOWS:

1. The process of producing a sustained release pharmaceutical composition of a solid medical material which comprises dissolving a solid medical material and at least one substance selected from a first group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate meta-acrylic acid copolymer, 2-methyl-5-vinyl-pyridin-methyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acid in water or an organic solvent, distilling off the solvent and adding polyethylene oxide.

2. The process of claim 1, further comprising dissolving with said solid medical material and the selected one or more substances from said first group at least one substance selected from a second group consisting of surface active agent, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid ester and vegetable oil in water or an organic solvent, distilling off the solvent and then adding polyethylene oxide.

3. The process of claim 1, which comprises dissolving said solid medical material and the selected one or more substance from said first group with polyethylene oxide in water or an organic solvent and distilling off the solvent.

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4. The process of claim 2, which comprises dissolving said solid medical material, the one or more selected substances from each of said first and second group with polyethylene oxide in water or an organic solvent and distilling off the solvent.

5. A process for producing a sustained release pharmaceutical composition of nicardipine or a salt thereof comprising compounding amorphous nicardipine or its salt in fine powder form with a fine powder of polyethylene oxide.

6. The process of claim 5, wherein amorphous nicardipine or its salt is that obtained by friction pulverizing to fine powder.

7. The process of claim 6, wherein the friction pulverizing is performed with a ball mill or a vibrating ball mill.

8. A sustained release pharmaceutical composition comprising amorphous nicardipine or its salt in fine powder form compounded with a fine powder form of polyethylene oxide.

1           The present invention relates to a process of producing sustained release pharmaceutical composition of a solid medical material.

          A sustained release pharmaceutical composition has many advantages in medical viewpoint such as the reduction of administration times, the decrease of side effects, the sustentation of effective concentration of medical material in blood. Therefore, various sustained release pharmaceutical compositions have hitherto been developed, for example a  
10   pharmaceutical composition containing great amount of excipient which is difficult to be disintegrated in stomach or intestines, a pharmaceutical composition in the form of a granule or tablet coated with repellent, a pharmaceutical composition filmed with semipermeable membrane, a pharmaceutical composition in which a polymer having low solubility or being hydrophylic is mixed with, absorbed in or combined with a medical material to gradually release medical material. As the polymer using for this purpose, there are acid-type carboxyvinyl polymer, polyvinyl alcohol, polyacrylic acid,  
20   etc. However, a sustained release pharmaceutical composition usually cannot avoid lowering the bioavailability accompanied with the sustaining release effect. Particularly, in the case of that a medical material itself has low solubility, sometimes the constant effective concentration of a medical material in blood cannot be obtained. Accordingly, for such medical material, it has been greatly desired to obtain a pharmaceutical composition which possess high solubility and superior sustained release activity.

          Under these circumstances, the inventors of the present

1 invention have found that a pharmaceutical composition having high solubility and superior sustained release activity can be obtained by containing a medical material in amorphous form.

That is, the object of the present invention is to provide a process of producing pharmaceutical composition having high solubility and superior sustained release activity by containing amorphous medical material, polyethylene oxide, and at least one basic substance (1st component) selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal diethylaminoacetate, dimethylaminoethyl meta-acrylate meta-acrylic acid copolymer, 2-methyl-5-vinylpyridinemethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acid. This pharmaceutical composition may further contain at least one basic substance (2nd component) selected from the group consisting of surface active agent, polyethylene glycol, propylene glycol, glycerin, glycerin fatty acid ester and vegetable oil.

20 As the result of the further investigation of the pharmaceutical composition of nicardipine (chemical name: 2,6-dimethyl-4-(3'-nitrophenyl)-1,4-dihydropyridin-3,5-dicarboxylic acid-3-methyl ester 5- $\beta$ -(N-benzyl-N-methylamino)-ethyl ester) among the above solid medical material, the inventors of the present invention have found that a sustained release pharmaceutical composition of nicardipine can be obtained by using amorphous nicardipine or its salt without the addition of any other

1           Accordingly, the other object of the present invention  
is to provide a process of producing sustained release  
pharmaceutical composition of nicardipine which contains  
amorphous nicardipine or its salt. This pharmaceutical  
composition need not contain the above 1st components as  
well as 2nd components to possess the sustained release  
activity, but if desired, it can contain such substances.

          The sustained release pharmaceutical composition of a  
solid medical material of the first object of the present  
10 invention can be obtained by the following method.

          A solid medical material and the above basic substance(s),  
that is, the 1st component(s) or the 1st component(s) and  
the 2nd component(s) are dissolved in an organic solvent  
such as methanol, ethanol, chloroform, dichloromethane,  
singly or in a combination thereof, or water, and then the  
solvent is removed. The removal of the solvent is carried  
out by drying under reduced or normal pressure, spray drying,  
fluidized-bed granulating drying, or lyophilization, etc.  
By the above procedures, the fine powder or fine particle  
20 granules are obtained in which a solid medical material is  
dissolved or dispersed uniformly in amorphous form in the  
basic substance(s). Then, polyethylene oxide is added to  
the fine powder or fine particle granules thus obtained  
followed by mixing them to provide the sustained release  
pharmaceutical composition of the present invention.

          This pharmaceutical composition also can be obtained  
by adding polyethylene oxide and the basic substance(s),  
that is, the 1st component(s) or the 1st component(s) and  
2nd component(s) simultaneously, wherein polyethylene oxide

1 material in the basic substance(s).

As the solid medical material in the present invention, any medical material having low or high solubility can be used if desired to keep in gastro-enteric tracts for long time. And the examples thereof are nicardipine hydrochloride, nifedipine, indenerol, indomethacin, buformin hydrochloride, etc.

10 As the amino acid of the 1st component, there are threonine, glycine, alanine, cysteine, lysine, etc. As the surface active agent of 2nd substance, there are anionic surface active agent such as sodium alkylsulfate, non-ionic surface active agent such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene castor oil derivative, etc. And as the vegetable oil, there are sesame oil, corn oil, soybean oil, rapeseed oil, olive oil, coconut oil, etc.

20 The compounding ratio of each component in the pharmaceutical composition vary according to the kind of a solid medical material or its administration dose. Usually, it is proper to use 0.5 - 20 parts by weight, preferably 1 - 10 parts by weight of the 1st component(s), 0.05 - 10 parts by weight, preferably 0.1 - 5 parts by weight of the 2nd component(s), per one part by weight of a solid medical material. The compounding ratio of polyethylene oxide is properly 0.1 - 50 parts by weight, preferably 0.5 - 30 parts by weight, per one part by weight of total amount of the solid medical material, the 1st component(s) and the 2nd component(s).

The sustained release pharmaceutical composition thus



1 in which a solid medical material is contained in the  
amorphous form. Hitherto, polyethylene oxide has been used as  
a coating agent or a binder in the preparation of  
pharmaceutical compositions, but it has not been reported that  
a sustained release pharmaceutical composition can be obtained  
by compounding polyethylene oxide with a solid medical  
material in amorphous form such as the present invention. And  
the sustained release pharmaceutical composition of the  
present invention can provide not only the sustained release  
10 effect but the good absorbability of a medical material, so  
that it gives high bioavailability.

The pharmaceutical composition of the present invention  
can be practically used by formulating to powders, granules,  
tablets, pills, capsules by a conventional manner. In the  
preparation of such formulations, there may be used a diluting  
agent, binder, viscosity-increasing agent, etc.,  
conventionally used. Further, according to the kind of a  
solid medical material, a compound for dissolving quickly the  
medical material can be added in the pharmaceutical  
20 composition or the treatment for dissolving the composition in  
the intestines can be applied.

As mentioned above, the other object of the present  
invention is to provide a sustained release pharmaceutical  
composition of nicardipine which possesses the coronary and  
cerebral vascular dilator activity and are useful for curing  
cerebral vascular disease, hypertension and angina pectoris.  
Hitherto, it has been difficult to provide a sustained release  
pharmaceutical composition of nicardipine because of its low  
solubility in intestines. That is, nicardipine or its salt  
30 can be easily dissolved in the first liquid (artificial

1 gastric juice) of Japanese Pharmaceopeia, so that it gives  
sufficiently the medical activity by usual formulations, but  
is slightly dissolved in the second liquid (artificial  
intestinal juice).

Under these circumstances, the inventors of the present  
invention have found that a sustained release pharmaceutical  
composition of nicardipine can be obtained by using amorphous  
nicardipine without adding any substance improving the  
solubility in the intestines. This composition can constantly  
10 sustain the effective concentration of nicardipine in blood  
for a long period of time as having superior absorbability to  
intestinal tract membrane in spite of low solubility of  
nicardipine in the intestinal juice.

Amorphous nicardipine used in the present invention can  
be prepared by friction-pulverizing the powder of nicardipine,  
preferably, by pulverizing the powder of nicardipine to fine  
powder using a ball mill or a vibrating ball mill.

In the pulverizing step, it is desired to add some  
substances to decrease the adherence and massing of nicardi-  
20 pine so that nicardipine can be completely pulverized to fine  
powder. Examples of such substances are calcium lactate, TC-5  
(trademark) available from Shinetsu Kagaku Kogyo Co.,  
ingredient: hydroxypropylmethyl cellulose, Avicel (trademark)  
available from Asahikasei Kogyo Co., ingredient: crystalline  
cellulose. The change of nicardipine or its salt to the  
amorphous form in the pulverizing step can be confirmed by  
X-ray diffraction.

The compound ratio of the powder of nicardipine can be  
properly controlled, and usually 5-90%, preferably 10-70%,  
30 more preferably 20-40% in the total weight of the  
composition. The powder of nicardipine is usually in the

1       crystalline form, for example, nicardipine hydrochloride is a  
crystal having a melting point of 168-170 degrees C. But, it  
can be possible to produce amorphous nicardipine in the  
synthesis step or purification step of nicardipine, and in  
that case the formed amorphous nicardipine can be used as it  
is for preparing the composition of the present invention.

          The fine powder of amorphous nicardipine in the present  
invention can give the sustained release effect only by  
applying some coating to avoid the disintegration and  
10       dissolution in stomach. And further it can give such effect  
by adding a pH-depending agent, a viscosity-increasing agent  
or a water-insoluble agent before or after the pulverizing  
step.

          As the pH-depending agent, there are the bases soluble  
in the intestines such as cellulose acetate phthalate,  
hydroxypropylmethyl cellulose, Eudragit L,S,RL and RS  
(trademark) available from Rohm and Hass Co., ingredient:  
acrylic acid metal-acrylic ester copolymer, or meta-acrylic  
acid meta-acrylic acid ester copolymer. As the viscosity-  
20       increasing agent, there are polyethylene oxide, Carbopol  
(trademark) available from B.F. Goodrich Co., ingredient:  
carboxyvinyl polymer, sodium polyacrylate, sodium arginate,  
carboxymethyl cellulose calcium, carboxymethyl cellulose  
sodium, polyethylene glycol (molecular weight: 6000-20000).  
And as the water-insoluble agent, there are crystalline  
cellulose for example, Avicel (trademark) calcium phosphate,  
etc.

          The compound ratio of the above agents can be properly  
controlled according to the formulations practically used.

20       The adsorption amount of nicardipine can be controlled by the

1 of the above agents, so that it is possible to control the appearance of medical effect and effective time of nicardipine.

The pharmaceutical composition of the present invention is formulated to granules, tablets, pills, capsules, etc., by a conventional manner. In the preparation of these formulations, there can be added diluting agent, binder, ingrediating agent, etc., conventionally used.

Then, the present invention is explained in detail by the following Experiment and Examples.

#### 10 Experiment

Control:

After pulverizing the crystalline powder of nicardipine hydrochloride by sample mill (using 1 mm screen), mini tablets each weight of 35 mg were prepared by a conventional manner according to the following prescription. The tablets were coated with cellulose acetate phthalate the film of which is soluble in the intestines to provide the tablets soluble in the intestines:

#### Prescription

20	Nicardipine hydrochloride	5.0 mg
	Lactose	20.3 mg
	Corn starch	7.0 mg
	Hydroxypropyl cellulose	1.4 mg
	Carboxymethyl cellulose calcium	1.1 mg
	Magensium stearate	<u>0.2 mg</u>
		35.0 mg

Pharmaceutical composition of the present invention:

20 g of the crystalline powder of nicardipine hydrochloride, 4 g of TC-5 (trademark) and 38 g of Avicel

(trade name) were pulverized for 16 hours by a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. Using the powder thus obtained, the tablets each weight of 312 mg were prepared according to the following prescription, and they were coated with cellulose acetate phthalate to be dissolved in the intestines.

Prescription:

Nicardipine hydrochloride	40 mg
TC-5	8 mg
Avicel	76 mg
Particles 209 for direct compression (Fiji Kagaku Kogyo Co.)	120 mg
Carboxymethyl cellulose calcium	64 mg
Magnesium stearate	<u>4 mg</u>
	312 mg

Concentration in blood when orally administered to dogs:

<u>Sample</u>	<u>Control</u>	<u>Phrm. Com. of this invention</u>
Number of dog	6	6
Dose	5 mg/Kg	10 mg/Kg
1 hr.	7.7	103.0
2 hr.	6.9	156.1
3 hr.	3.4	127.7
4 hr.	1.3	89.0
6 hr.	0.1	141.7
8 hr.	9.2	55.9
10 hr.	-	56.0
12 hr.	-	35.4

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1           Example 1

1000 g of a mixture of dichloromethane and methanol (1 : 1 in weight ratio) was added to a mixture of 50 g of nicarpidine hydrochloride and 100 g of hydroxypropylmethyl cellulose to provide solution. The organic solvent of the solution was distilled off by spray-drying to provide fine particle powder. To 50 g of the fine particle powder thus obtained were added 30 g of the fine particle powder of polyethylene oxide and 3.3 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 250 mg of the mixture in No. 1 capsules.

Example 2

1000 g of dichloromethane was added to a mixture of 50 g of nifedipine, 50 g of polyethylene glycol 400 and 250 g of polyvinyl pyrrolidone to provide a solution, and 25 g of magnesium meta-silicate aluminate was dispersed uniformly in the solution. Using a fluidized-bed granulator, 350 g of anhydrous phosphoric acid hydrogen calcium was fluidized and sprayed with the above solution to provide fine granules. To 250 g of the fine granules thus obtained were added 89.5 g of the fine particle powder of polyethylene oxide, 7 g of talc and 3.5 g of magnesium stearate, and they are mixed uniformly. Tablets each weight of 350 mg were prepared using oblong punch having the major axis of 24 mm and the minor axis of 7 mm.

Example 3

3000 g of a mixture of dichloromethane and methanol (1 : 1 in weight ratio) was added to a mixture of 100 g of indomethacin, 300 g of hydroxypropyl cellulose and 20 g of polyethylene oxide to provide a solution. The organic solvent

1 fine particle powder. To 160 g of the fine particle powder thus obtained were added 80 g of polyethylene oxide and 10 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 250 mg of the mixture in No. 1 capsules.

#### Example 4

400 g of methanol was added to a mixture of 20 g of nicardipine hydrochloride, 40 g of hydroxypropylmethyl cellulose phthalate and 10 g of polysorbate 80 to provide  
10 a solution. The organic solvent of the solution was distilled off by drying under reduced pressure to provide a solid material. The solid material was pulverized to fine particle powder. To 35 g of the fine particle powder thus obtained were added 105 g of fine crystalline cellulose, 80 g of polyethylene oxide and 10 g of talc, and they were mixed uniformly. Capsules were prepared by filling each 230 mg of the mixture in No. 1 capsules.

#### Example 5

20 15 g of the crystalline powder of nicardipine hydrochloride, 3 g of TC-5 (trade name), 20.6 g of Avicel (trade name) and 18.2 g of HP-55 (trade name, Shinetsu Kagaku Kogyo Co., ingredient: hydroxypropylmethyl cellulose phthalate) were pulverized for 16 hours by a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to the amorphous form. Using the powder thus obtained, the tablets each weight of 500 mg were prepared according to the following prescription.

Prescription:

1	Avicel	103 mg
	HP-55	91 mg
	Particles 209 for direct compression	125 mg
	Carboxymethyl cellulose calcium	20 mg
	L-HPC (L-H31) *	66 mg
	Magnesium stearate	<u>5 mg</u>
		500 mg

\*L-HPC(L-H-31): trade name, Shinetsu Kagaku Kogyo Co.

ingredient: lower substituted hydroxy-  
propyl cellulose

#### Example 6

20 g of the crystalline powder of nicardipine hydrochloride, 20 g of polyvinyl pyrrolidone K-30 (trade name, BASF Co.), HP-55 (trade name) and 4 g of Carbopol-940 (trade name) were pulverized for 16 hours by a vibrating ball mill, whereby the crystals of nicardipine hydrochloride changed to amorphous form. Using the powder thus obtained, tablets each weight of 360 mg were prepared according to the following prescription.

#### Prescription:

20	Nicardipine hydrochloride	60 mg
	Polyvinyl pyrrolidone K-30	30 mg
	HP-55	180 mg
	Carbopol-940	12 mg
	Polyethylene glycol 6000	<u>48 mg</u>
		360 mg

#### Example 7

40 g of the crystalline powder of nicardipine hydrochloride, 200 g of calcium lactate and 20 g of polyethylene



1 mill, whereby the crystals of nicardipine hydrochloride  
 changed to amorphous form. Using fluidized-bed granulator  
 Uniglat (trademark) available from Okawara Seisakusho Co., 195  
 g of the powder thus obtained and 150 g of Kalica GS  
 (trademark) available from Kyowa Kagaku Kogyo Co., ingredient:  
 anhydrous phosphoric acid hydrogen calcium were fluidized,  
 sprayed with a solution of 20 g of polyethylene oxide-18 in  
 3000 ml of methylene chloride, and treated by a conventional  
 manner to provide fine granules. Capsules were prepared by  
 10 filling each 365 mg of the fine granules thus obtained in No.  
 1 capsules by a conventional manner.

#### Example 8

The crystalline powder of nicardipine hydrochloride, 80  
 g of Eudragit RL (trademark) available from Rohm and Hass Co.,  
 ingredient: acrylic acid meta-acrylic acid ester copolymer, 4  
 g of sodium arginate and 200 g of Avicel (trademark) were  
 pulverized for 16 hours by a vibrating ball mill, whereby the  
 crystals of nicardipine hydrochloride were changed to  
 amorphous form. Using the powder thus obtained, tablets each  
 20 weight of 600 mg were prepared according to the following  
 prescription.

#### Prescription:

Nicardipine hydrochloride	60 mg
Eudragit RL (trademark)	120 mg
Sodium arginate	6 mg
Avicel (trademark)	300 mg
Lactose	78 mg
Corn starch	30 mg
Magnesium stearate	<u>6 mg</u>
	600 mg

1            50 g of the crystalline powder of nicardipine hydro-  
chloride and 250 g of TC-5 (trade name) were pulverized for  
16 hours by a vibrating ball mill, whereby the crystals of  
nicardipine hydrochloride changed to amorphous form. To 120 g  
of the powder thus obtained were added 140 g of lactose and  
150 g of Avicel (trade name), and they were mixed uniformly.  
The mixed powder thus obtained was rotated in a coating pan  
used in usual sugar coating, and sprayed with a solution of  
10 g of methyl cellulose in 1000 g of water to provide pills  
10 of 32 - 18 mesh. The half amount of the pills thus obtained  
were recovered, and the remained half amount of the pills were  
further rotated in the same coating pan and sprayed with a  
solution of 10 g of Eudragit RL (trade name) in a mixture  
of 70 g of acetone and 130 g of isopropanol. Then, whole  
pills were combined and mixed uniformly. Capsules were  
prepared by filling each 450 mg of the mixture in No. 0  
capsules.

**SUBSTITUTE**

***REMPLACEMENT***

**SECTION is not Present**

***Cette Section est Absente***